REVIEW

Complement inhibition by gram-positive pathogens: molecular mechanisms and therapeutic implications

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Abstract The plasma proteins of the complement system are essential in the innate immune response against bacteria. Complement labels bacteria with opsonins to support phagocytosis and generates chemoattractants to attract phagocytes to the site of infection. In turn, bacterial human pathogens have evolved different strategies to specifically impair the complement response. Here, we review the large arsenal of complement inhibitors produced by the gram-positive pathogens *Staphylococcus aureus* and Group A *Streptococcus*. We discuss how these bacterial molecules provide us with new tools to treat both infectious and inflammatory disease conditions in humans.

**Keywords** Complement · Immune evasion · Bacteria · Innate immunity

The innate immune system plays a critical role in our host defense against invading pathogens. This system consists of three different parts: (a) the complement system, (b) phagocytes, and (c) antimicrobial peptides. The three major functions of the complement cascade in innate immunity are (1) to label pathogens or immunogenic particles with C3b and iC3b to facilitate phagocytic uptake via complement receptors, (2) to attract phagocytes by producing chemoattractant C5a, and (3) to directly lyse gram-negative

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bacteria through membrane attack complex (MAC; C5b-9) formation (Fig. 1) [1]. Complement is initiated by two specific recognition pathways, the classical and lectin pathway, which are amplified by the alternative pathway. All three pathways converge at the formation of the C3 convertases. These bimolecular surface-bound enzyme complexes catalyze the key reaction in complement activation: cleavage of complement protein C3 into C3a, a chemoattractant with bactericidal activity [2–4], and C3b [5]. Convertase formation is pivotal in complement activation since C3b and its inactive derivative iC3b facilitate phagocytosis. Furthermore, the deposited C3b can form new convertases, thereby amplifying the opsonization process. Subsequently, the high concentrations of locally deposited C3b induce a shift in substrate specificity of the convertase to complement protein C5. The cleavage products of C5 are C5a, a potent chemoattractant, and C5b that initiates the lytic pathway. Due to the resulting C5a gradient, neutrophils migrate toward the site of infection and phagocytose the invaders. Neutrophils kill ingested particles intracellularly by the production of reactive oxygen species and the release of granule constituents such as proteolytic enzymes and antimicrobial peptides. These peptides are also released into the extracellular space to kill microorganisms extracellularly [6]. Together, these complement-mediated events are responsible for the efficient elimination of invading bacteria.

It has become increasingly evident that pathogens have developed various ways to evade the constant attack of the complement system. Pathogens produce proteins that modulate all stages of the complement cascade. These proteins inhibit complement recognition and amplification, cleave complement proteins, or interfere with complement receptor interactions on phagocytes. A number of reviews have been published on these specific topics [7–9]. In this
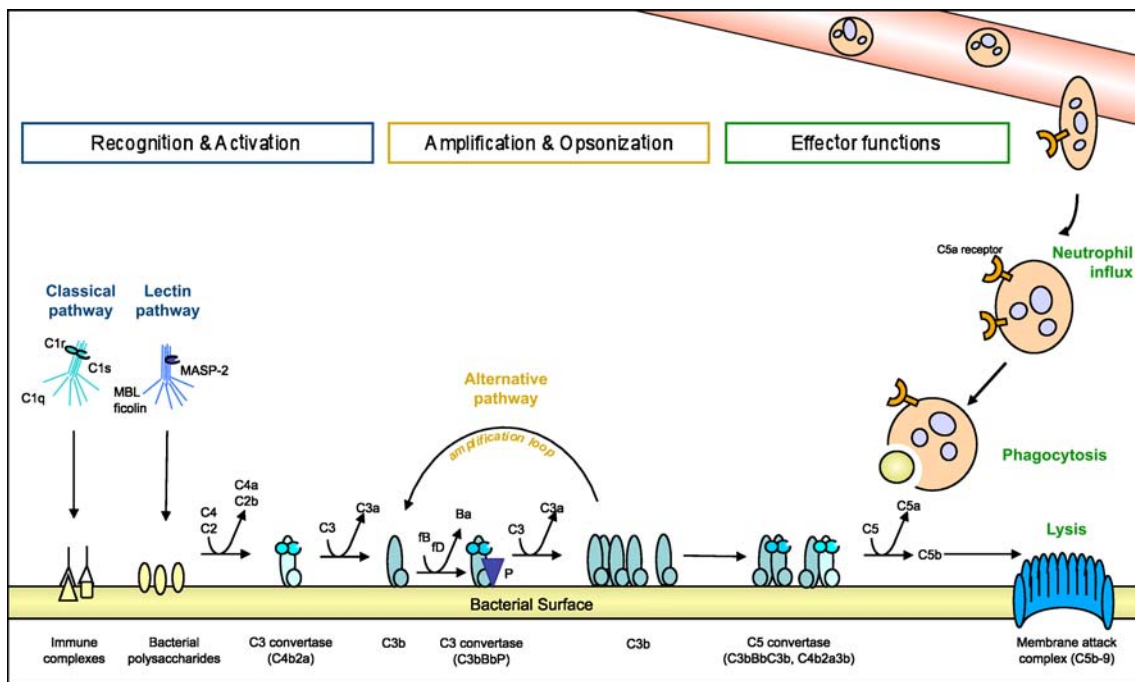
Fig. 1 Schematic overview of the complement system. The complement cascade is activated by recognition of microbe-bound antibodies or microbial sugars by the C1 complex (CP) or the MBL- and ficolin-MASP-2 complex (LP), respectively. Both C1s and MASP-2 cleave complement proteins C4 and C2 to generate the CP/LP C3 convertase: C4b2a. The *Alternative Pathway* (AP) C3 convertase C3bBb is generated after binding of fB to surface-bound C3b and subsequent cleavage by fD. The AP C3 convertase is stabilized by the positive regulator human properdin [47, 48]. Both C3 convertases (*C4b2a* and *C3bBb*) cleave C3 into C3a and C3b. C3b covalently binds to bacterial surfaces, thereby amplifying complement activation through formation of new C3 convertases and contributes to phagocytosis, antigen presentation, and formation of C5 convertases (*C4b2a3b* and *C3bBb3b*). C5 convertases cleave C5 into the anaphylatoxin C5a, which attracts neutrophils to the site of infection, and C5b, which forms a complex with complement proteins C6–C9 to generate the membrane attack complex

paper, we give a broad overview of the complement evasion strategies of the two most important gram-positive human pathogens *Staphylococcus aureus* and group A *Streptococcus* (GAS), and we discuss the potential of these bacterial complement modulators as therapeutic agents.

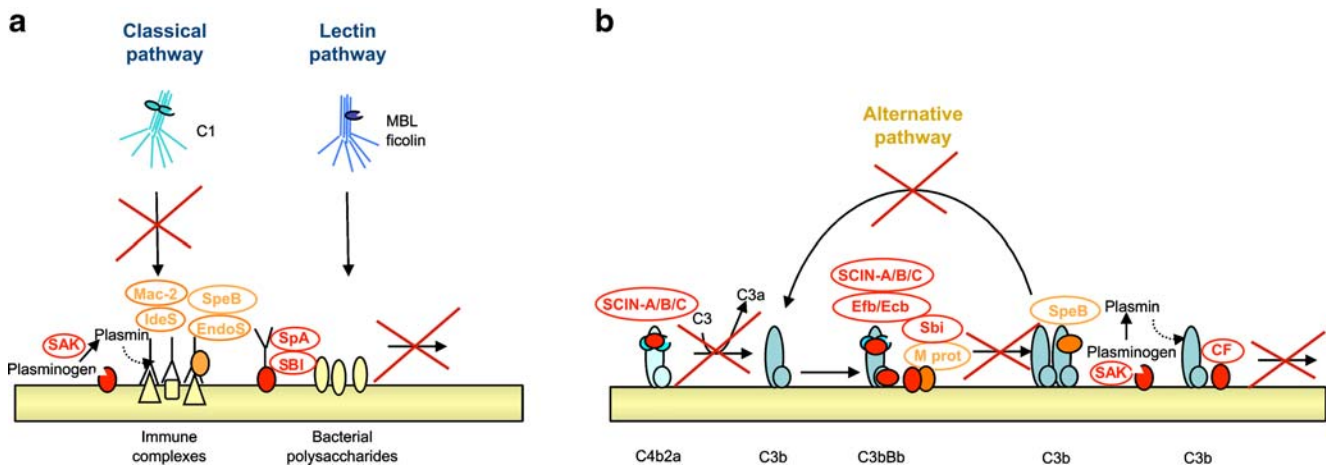## Modulation of complement recognition and activation

The classical and lectin pathways of complement ensure immediate recognition of invading bacteria as nonself. The C1-complex (classical pathway) recognizes bacterium-bound IgG and IgM while mannose-binding lectins and ficolins (lectin pathway) bind bacterial sugar moieties. *S. aureus* expresses two surface-anchored proteins that impair IgG function (Fig. 2a): staphylococcal protein A (SpA) and staphylococcal immunoglobulin-binding protein (Sbi). SpA is a surface protein with four or five immunoglobulin-binding repeat domains. Each domain can bind the Fc-part of IgG, thereby blocking the interaction with Fc receptors on neutrophils in vitro [10, 11]. Sbi consists of four small domains, of which two (Sbi-I and Sbi-II) can bind IgG [12]. Next to blocking Fc-receptor-mediated phagocytosis, Sbi

has been suggested to block binding of C1q and subsequent activation of the classical pathway.

Another strategy to prevent recognition is to eliminate opsonic molecules from the bacterial surface by proteolytic degradation. Staphylokinase (SAK) is a secreted protein that binds and activates surface-bound plasminogen into plasmin, which may enhance bacterial invasion through host tissues. Interestingly, it has been shown that SAK is anti-opsonic as well. SAK-mediated plasmin deposition on the bacterial surface can cleave IgG and C3b and thereby inhibit phagocytosis in vitro [13]. GAS expresses several proteases that directly cleave IgG: the Endoglycosidase in *Streptococcus pyogenes* (EndoS) specifically hydrolyzes the asparagine-linked glycan in the C_H2 domain of IgG; the IgG-degrading enzyme of *S. pyogenes* (IdeS or Mac-1), Mac-2, and streptococcal pyrogenic exotoxin B (SpeB) all cleave IgG in the hinge region [14, 15].

Modulation of complement amplification

Formation of the C3 convertases is elemental for amplification of complement activation and downstream immune

Fig. 2 Bacterial evasion of complement recognition (**a**) and opsonization (**b**). Illustrated are proteins of *S. aureus* (*red*) and GAS (*yellow*) that modulate complement recognition and opsonization. **a** To prevent recognition by the classical pathway, *S. aureus* expresses the surface proteins ProtA and Sbi. Both proteins bind the Fc tail of IgG preventing its interaction with FcR on neutrophils. Another mechanism to prevent recognition is by inactivating IgG, either directly by proteases IdeS, Mac-2, and SpeB, or indirectly by SAK-activated plasmin. **b** There are three ways by which *S. aureus* and GAS modulate opsonization: (1) C3 cleavage; directly by SpeB or indirectly by SAK-mediated activated plasmin. ClfA binds human fI, thereby enhancing C3 cleavage. (2) Convertase modulation; *S. aureus* inactivates the C3 convertases by secreting SCIN, SCIN-B, SCIN-C, Efb, and Ecb. (3) Modulating host regulators; Sbi and the streptococcal M-protein bind the negative convertase regulators (human FH, FHL1, C4BP, and CD46) while SpeB cleaves the positive convertase regulator, properdin

responses. There are three ways by which *S. aureus* and GAS modulate this central step in the complement cascade (Fig. 2b):

1. Cleavage of C3

The abundant GAS protease SpeB is, next to cleaving IgG, involved in breakdown of C3. Comparison of wild-type GAS and a SpeB knockout showed that SpeB blocks neutrophil recruitment to the site of infection and subsequent phagocytosis and bacterial clearance in vivo [16, 17]. The *S. aureus* surface protein clumping factor A (ClfA) can bind the human C3b protease factor I (fI), thereby enhancing cleavage of surface-bound C3b into iC3b in vitro [18].

2. Direct inactivation of C3 convertases

Convertases are the major complement target among *S. aureus* immune evasion strategies. *S. aureus* secretes five different molecules that directly inhibit these central enzyme complexes. Staphylococcal complement inhibitor (SCIN) and its homologues SCIN-B and SCIN-C are highly effective C3 convertase inhibitors that block conversion of C3 and subsequent phagocytosis and C5a formation in vitro at low concentrations [19]. The alternative pathway C3 convertase consists of a cofactor (C3b) which is loosely bound to the protease subunit (Bb). Recent structural studies revealed that the small 10-kD SCIN protein fixates the convertase conformation and as such hampers a critical rearrangement of the protease subunit Bb in relation to substrate C3 [20, 21]. The action of SCIN on the classical pathway convertase remains to be resolved but seems to be caused by a stabilizing mechanism as well [19]. Extracellular fibrinogen-binding protein (Efb) and extracellular complement-binding protein (Ecb) can modulate the alternative pathway convertase by binding to the C3b molecule directly [22]. The crystal structures of both molecules in complex with the C3d domain of C3 have revealed their exact binding sites [23, 24]. Interestingly, since the C3d fragment of C3 is involved in stimulation of adaptive immune responses, it was recently suggested that Efb functions as an adaptive immunity modulator as well [25].

3. Binding or cleavage of human convertase regulators

To protect host tissues from excessive complement activity, humans express complement regulators that down-regulate convertase activity. A large number of pathogens express molecules that attract these regulators to their surface. The staphylococcal IgG-binding molecule Sbi has a diverse role in complement modulation. Next to its two IgG-binding domains, Sbi-III and IV, it can also bind to C3 [26]. Furthermore, Sbi binds the human complement regulators factor H (FH) and factor H-related proteins and can form a stable tripartite complex with C3 and FH [27]. Altogether, these actions result in inhibition of the alternative pathway in vitro. The streptococcal M protein is a multifunctional surface molecule that binds four different human convertase regulators: FH, factor H like-1 (FHL1), membrane cofactor protein (CD46), and C4-binding protein (C4BP). M protein consists of two polypeptide chains configured in an alpha-helical coiled coil complex that is anchored to the cell membrane via its C terminus [28–30]. From the N to the C

terminus, the protein comprises four repeat regions: hypervariable (a), variable (b), and conserved (c and d). Depending on the M type, the hypervariable region can bind FH, FHL-1 [31], and C4BP [32]. By binding these complement regulators, M protein limits deposition of C4b and C3b increasing GAS resistance to phagocytosis [33]. In vivo studies with strains expressing mutated M protein indicate that protein is an important GAS virulent factor [34]. Finally, SpeB also digests the positive convertase regulator properdin, making the streptococci more resistant to neutrophil killing in vitro [35].

## Modulation of the complement effector functions: inhibiting C5 activation and neutrophil migration

In the final step of the complement cascade, the C5 convertases cleave C5 to generate the important chemoattractant C5a that directs neutrophils to the site of infection. *S. aureus* and GAS use various approaches to evade the C5a-mediated immune responses (Fig. 3). Staphylococcal superantigen-like 7 (SSL7) is a secreted protein that specifically binds to C5 [36] and thereby prevents C5 activation into C5b and C5a in vitro (J. Bestebroer, personal communication). Efb and Ecb are very potent inhibitors of C5a responses in vitro and in vivo [22]. These molecules elicit their immune modulating capacity by binding the C3b part of the C5 convertase complex. GAS uses the cell-associated peptidase ScpA to directly target C5a. ScpA cleaves C5a and blocks chemotaxis of phagocytes toward the site of infection [37]. In a mouse pneumonia model, it was shown that the ScpA knockout mutant was less virulent than wild-type GAS [38]. Modulation of C5a responses by *S. aureus* proceeds through inhibition of the C5a receptor (C5aR). The chemotaxis inhibitory protein of *S. aureus* (CHIPS) is a 14-kD excreted protein that effectively blocks neutrophil recruitment toward C5a in vitro by binding the C5aR with high (nanomolar) affinity [39]. The recent nuclear magnetic resonance (NMR) structure of CHIPS in complex with the N terminus of the C5aR showed two sulfated tyrosine (residues 11 and 14) of the C5aR to be essential for the interaction in between the C5aR and the inhibitor CHIPS [40].

Cleavage of C5 also results in formation of C5b, the molecule that initiates the formation of the membrane attack complex (C5b-9). This complex can damage target cells such as gram-negative bacteria. MAC formation is often monitored in vitro by a so-called hemolytic assay in which erythrocytes (often sheep or rabbit) are used as a direct target for complement activation and hemolysis. The *S. aureus* proteins SCIN, Efb, Ecb, and SSL7 block MAC-mediated erythrocyte hemolysis since they inhibit the complement cascade upstream of MAC formation. The highly variable strepto-

coccal inhibitor of complement (SIC) from GAS was found to specifically block formation of the MAC by binding to the C5b-7 complex and preventing erythrocyte hemolysis in vitro [41]. The relevance of MAC inhibition by grampositive bacteria remains unclear since they are naturally protected from lysis via their thick cell wall. The SIC molecule also interacts with several human antimicrobial peptides (LL-37, defensins) [42], and this might be more relevant for protecting GAS from host immunity.

Complement evasion molecules as tools and targets in therapy

Bacterial complement modulators have important applications for the treatment of inflammatory diseases where complement is directed against our own cells [43]. Per definition, molecules that counteract acute innate immune
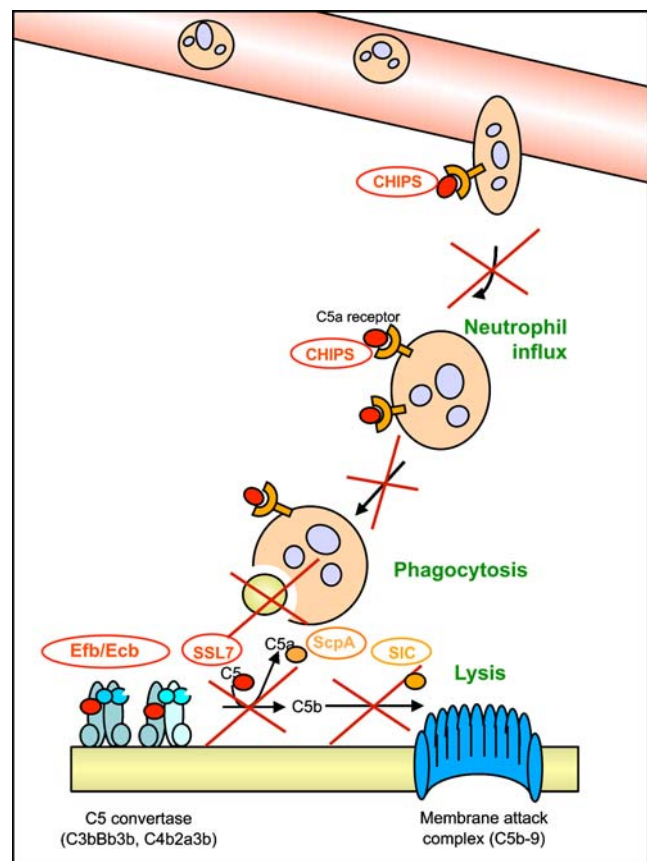
Fig. 3 Bacterial evasion of C5-mediated responses. Illustrated are proteins of *S. aureus* (*red*) and GAS (*yellow*) that modulate C5-mediated responses. Efb and Ecb block the formation of C5 convertases and thereby inhibit C5a and MAC generation. SSL7 binds to C5 and prevents the cleavage of C5 into C5a and C5b. Neutrophil influx and phagocytosis are inhibited by CHIPS, which binds the C5aR, and ScpA that cleaves C5a. SIC inhibits the formation of the MAC, the final step in the complement cascade

mechanisms are anti-inflammatory compounds. As opposed to several bacterial toxins, the high specificity and the mode of action that depends entirely on protein–protein interactions makes these nontoxic proteins suitable anti-inflammatory drugs. It is tempting to speculate that these molecules could be used as injectables in acute inflammatory disorders. However, since these molecules are derived from common human pathogens, pre-existing antibodies severely complicate this approach. Furthermore, a number of the described molecules appear to be human-specific which complicates functional studies in vivo [19, 44, 45] However, the immunological molecules that are attacked by these factors might prove to be the essential targets to tackle in anti-inflammatory therapy. We feel that the bacterial products could be used as an indicator of the "Achilles heel" of the human immune system—almost at the atomic level. Especially, since the 3-D structures of a number of molecules in context with their target are now elucidated in several crystallographic and NMR studies [19, 20, 25, 40, 46], this opens new possibilities for smart design of small-molecule therapeutics. Thus, we can copy these evolutionary-designed molecules to counteract the detrimental effects of complement activation in inflammatory disease states.

Next to their potential as anti-inflammatory compounds, we believe that targeting of complement evasion molecules should be included in future strategies to fight bacterial infections. The evasion molecules described above not only suppress natural immunity during an infection but also hamper the current attempts to create effective vaccines. The efficacy of vaccines is held back by the existing bacterial immune evasion strategies since they prevent neutrophils or complement to reach the site of infection. Even with sufficient opsonic or bactericidal antibodies on the bacterium, nothing will happen if the innate immune effectors are absent. Since immune evasion molecules are essentially vaccine evasion molecules, we propose that these molecules should be specifically targeted in the vaccine. Alternatively, we could think of ways to neutralize these molecules and use that in novel strategies to fight infectious diseases. In fact, we propose to inhibit the inhibitor and thereby decrease the advantage of the bacterium over the host.

So, taken together, the smart attack of the bacteria on our complement system might hold clues for future drugs in both inflammatory as well as infectious diseases. In this way, we could turn this powerful escape mechanism into our own advantage.

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